

Radiation-associated venous stenosis: Endovascular treatment options

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We report a case of radiation-induced venous stenosis after pelvic irradiation to treat Paget's disease of the scrotum. During therapeutic anticoagulation, significant left lower extremity swelling developed due to an iliofemoral deep venous thrombosis (DVT). After percutaneous thrombectomy and thrombolysis, a high-grade stenosis was uncovered in the left external iliac vein, which was treated with an endoluminal stent. However, ipsilateral DVT recurred 2 months later despite continued anticoagulation therapy. Repeat treatment was successful. Pelvic radiation is a potential cause of iliac vein stenosis. Pharmacomechanical thrombectomy may have a useful role in management of complex iliofemoral DVT. (*J Vasc Surg* 2004;40:179-82.)

Although radiation-induced arteritis is a well-described disease, radiation-induced vasculitis involving the iliac veins is unusual. The treatment of complicated radiation-induced venous stenosis may be challenging. Traditional conservative therapy with anticoagulation may not be effective, because of an underlying anatomic defect, and symptoms may recur despite successful treatment. It is essential to recognize this dilemma and initiate appropriate management. Endovascular intervention provides an effective method for clot extraction, with the potential to reveal an inciting venous defect. The case presented illustrates both pelvic radiation as a potential cause of iliac vein stenosis and the useful role of percutaneous mechanical thrombectomy and thrombolysis in management of complex iliofemoral deep venous thrombosis (DVT).

CASE REPORT

A 75-year-old man received pelvic radiation to treat Paget's disease of the scrotum. Subsequent periodic examinations by an oncologist demonstrated no evidence of recurrent disease. However, 16 months after radiation therapy the patient had progressive left lower extremity swelling. At this time he was receiving therapeutic anticoagulation with warfarin sodium because of atrial fibrillation. At physical examination the left leg was tender, edematous, and erythematous, with signs of early phlegmasia. Duplex ultrasound scans demonstrated extensive iliofemoral DVT. A hypercoagulation evaluation did not reveal any abnormalities (laboratory tests included protein C and S, homocysteine, factor V Leiden, antithrombin, prothrombin mutation 20210, fibrinogen, lupus

anticoagulant, and anticardiolipin antibody). The patient was taken to the interventional suite for further imaging studies.

Venograms demonstrated total occlusion of the left common femoral vein and external iliac vein (EIV), with no filling of collateral vessels, thus indicating acute occlusion (Figs 1 and 2). A vena cava filter (Gunther-Tulip; Cook) was deployed through the contralateral femoral vein. Pharmacomechanical thrombectomy (PMT) was performed with a 6F AngioJet rheolytic thrombectomy catheter (Possis) inserted through the ipsilateral popliteal vein, with the patient prone. Two milligrams of tissue plasminogen activator (tPA) was added to the saline solution bag (AngioJet infusion solution) to increase clot removal capacity. The common femoral vein and EIV were patent on completion venograms, albeit with sluggish flow. Therefore overnight catheter-directed thrombolysis (tPA, 1 mg/hr for 4 hours, then 0.5 mg/hr) was performed. The lytic agent was discontinued 24 hours later after no improvement was seen. However, a high-grade EIV stenosis was revealed and successfully treated with angioplasty (Fig 3), and a 14-mm Wallstent (Boston Scientific) was deployed. After stent placement the flow improved dramatically. The patient was discharged to home receiving warfarin therapy, with complete symptom resolution.

Two months later the patient had extensive recurrent left iliofemoral DVT while receiving therapeutic anticoagulation with warfarin. Repeat PMT revealed in-stent stenosis of the previously placed EIV stent. A second 14-mm Wallstent was deployed across the lesion, with excellent angiographic results (Fig 4). The patient ultimately had a full and uneventful recovery. Subsequently the patient underwent extensive diagnostic evaluation including abdominal and pelvic computed tomography, colonoscopy, and echocardiography. There was no evidence of extrinsic compression (Fig 5), occult malignancy, or embolic source. Elaborate laboratory studies, including hypercoagulation evaluation and carcinoembryonic antigen level, also yielded normal results. At 18 months post-intervention the patient had no symptoms, with no further recurrence.

DISCUSSION

Radiation therapy has been extensively used as an adjunctive treatment for many cancers. Radiation-induced arteritis is a well-recognized entity with little known pathogenesis.¹⁻⁵ However, radiation-induced venous stenosis is

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Competition of interest: none.

Presented at the Twenty-eighth Annual Meeting of the Southern Association for Vascular Surgery, Rio Grande, PR, Jan 14-17, 2004.

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0741-5214/\$30.00

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doi:10.1016/j.jvs.2004.03.039



Fig 1. Initial venogram demonstrating large thrombus burden in iliac venous system.

extremely rare, with only a few cases reported in the literature.⁶⁻⁸ Existing cases mainly describe symptoms related to upper extremity venous stenosis or superior vena cava (SVC) syndrome. For example, Schreiber and Kapp⁹ reported four patients with upper extremity DVT after chemoradiation therapy for lymphoma, and theorized that radiation therapy was a contributing factor for DVT in these patients. Subsequently Van Putten et al¹⁰ reported two patients with venous fibrosis presenting as SVC obstruction after remote radiotherapy. In another case reported by Franklin et al¹¹ a patient had unilateral deep femoral vein stenosis 4 years after radiation therapy for malignant melanoma. Our case provides a valuable addition to this small literature collection.

The pathogenesis of radiation-induced vasculopathy has been studied, but not well-characterized. The proposed mechanism of disease process is presumed to be analogous to arteritis induced by radiation. In the early inflammatory phase endothelial cell swelling and sloughing characterize radiation-induced damage. In the later phases endothelial cell and smooth muscle cell proliferation contribute to vessel stenosis and thrombosis.¹² Knighton et al⁶ reported that macrophages secrete angiogenic factors in responding to tissue oxygen tension, and Zidar et al⁵ observed necrotizing vasculitis with significant changes in the vasa vasorum of the affected arteries in patients received radiation therapy

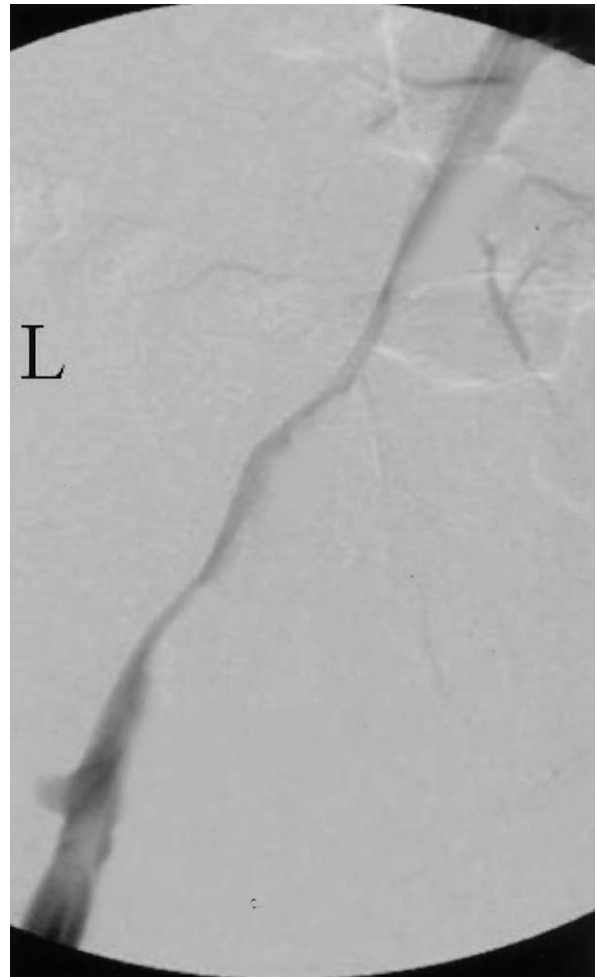


Fig 2. Initial ascending venogram, obtained via ipsilateral popliteal vein approach with patient prone, shows extensive deep venous thrombosis in external iliac vein (magnification, 720 × 540.)

for tonsil carcinoma. The findings of these authors support the hypothesis that injury to vasa vasorum creates a hypoxic condition that stimulates intimal proliferation. This is an important mechanism in the development of radiation-induced vasculopathy of large arteries. Furthermore, they suggest that injury to the vasa vasorum and the consequent ischemic lesions of the arterial wall are morphologic features that distinguish radiation-induced arterial injury from spontaneous atherosclerosis.⁵ Nevertheless, studies regarding effects of radiation on vessel walls have been controversial. Carter et al⁷ studied the long-term effects of radioactive stents on neointimal formation in swine coronary arteries. They concluded that continuous low-dose radiation delivered via phosphorus 32 radioactive stents promoted the formation of an “atheromatous” neointima after 6 months,⁷ and their previous study⁸ indicated that the response of vascular wall to radioactive stent was dose-dependent. In addition, Kelly et al¹³ demonstrated that external beam radiation therapy significantly reduces the amount of luminal stenosis at the graft-to-vein anastomotic

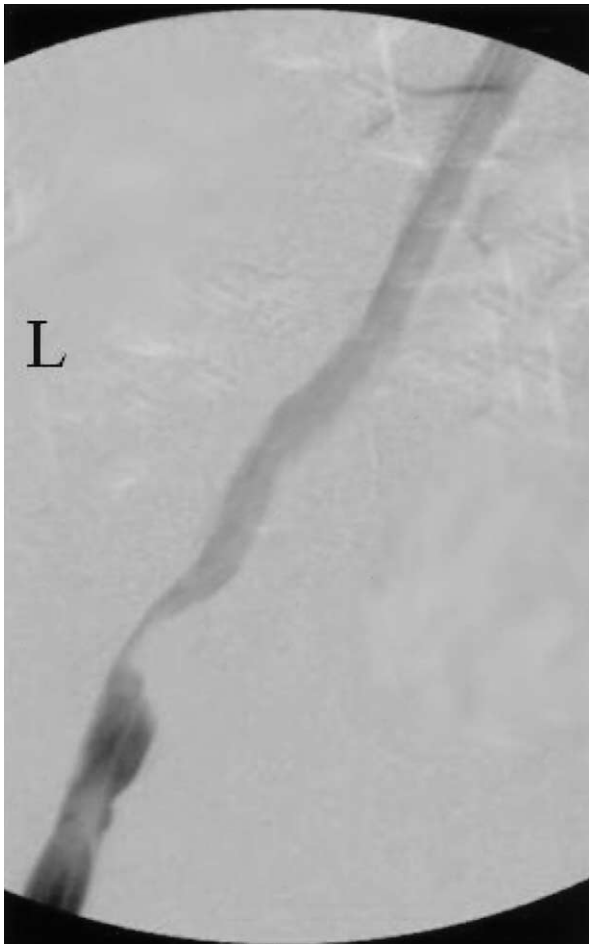


Fig 3. Venogram after pharmacomechanical thrombectomy and thrombolysis demonstrates segment of high-grade stenosis at left external iliac vein in area of radiation (magnification, 720×540).

site with minimal local and systemic toxicity in a pig model. The various results from multiple clinical and experimental trials suggest that the complex biologic interaction between radiation and the vascular wall has not been fully elucidated, and further exploration of the mechanism of radiation-induced venous stenosis is warranted. Both a lack of vasa vasorum and a paucity of smooth muscle in the vein wall make the existing proposed mechanisms for radiation-induced vasculopathy unlikely. This may also account for the relatively rapid time course for development of stenosis in our patient, inasmuch as radiation-induced arteritis usually is seen several years after radiotherapy. Because of the marked difference between venous and arterial anatomy, there is no definitive evidence as to whether radiation-induced venous stenosis will follow a similar time course as that of radiation-induced arterial stenosis.

Radiation-induced iliac venous stenosis may manifest with a variety of symptoms, from asymptomatic to extensive limb-threatening iliofemoral DVT or possibly life-threatening pulmonary embolus. Because of a venous wall anatomic defect, symptoms may not improve with conser-



Fig 4. Completion venogram after Wallstent placement (magnification, 720×540).

vative management. Occasionally symptoms may be temporarily palliated, but then recur as a result of impaired proximal venous outflow, as in our patient. Furthermore, it is not known whether radiotherapy inhibits collateral vessel formation. In a non-radiated field, as a vessel slowly occludes, collateral vessels dilate to provide compensatory circulation. Hypothetically, the radiation-induced stenosis along with a paucity of collateral vessels resulted in focal venous stasis, thrombosis, and subsequent occlusion. Data suggest that excessive radiation may decrease local levels of vascular endothelial growth factor and tumor necrosis factor- α , both factors known to be associated with intimal hyperplasia.¹⁴

Our patient had evidence of luminal narrowing, but lacked evidence of extrinsic compression such as surrounding tissue fibrosis, recurrence of disease, or lymphadeno-



Fig 5. Computed tomography scan shows no extrinsic compression. Arrow points to stent in left external iliac vein.

pathy. The second episode of DVT was likely predisposed by combined in-stent and native vessel stenosis. Because of the distal location of EIV stenosis, the first stent was intentionally deployed slightly high to avoid crossing the inguinal ligament. Even though the patient had excellent clinical and angiographic results at the end of the procedure, there was likely residual stenosis distal to the stent, which in combination with post-angioplasty recoil of the vessel caused venous thrombosis 2 months later.

The standard management of iliac venous stenosis has not been established. Most data are derived from SVC obstruction or upper extremity venous stenosis.^{6,7,10-12} Traditional surgical intervention involving thrombectomy or surgical bypass has been the main treatment of nonmalignant obstruction. Kalra et al¹⁵ compared endovascular and open surgical treatment of SVC obstruction in 32 patients, and concluded that surgical treatment has more long-term efficacy. Secondary endovascular interventions maintained graft patency and were effective over the short term, but repeat interventions were necessary. Endovascular treatment does not preclude future open surgical reconstruction, and may prove to be a reasonable primary intervention in selected patients, especially patients with malignancy. Clinical experience and reported cases in the literature demonstrate excellent outcomes with endovascular therapy. Quanadi et al¹⁶ deployed 15 Wallstents in 12 patients to treat SVC obstruction. The patients were followed up for a mean of 11 months, and all had successful recanalization of the occluded or stenotic segments. Carlson et al¹⁷ described 10 patients with pelvic vein stenosis that was also successfully treated with endovascular stents.

The only case in the literature describing endovascular treatment of radiation-induced venous stenosis involving the lower extremity is from Franklin et al.¹¹ Similarly, our case demonstrates the utility of multiple endovascular techniques in management of venous stenosis. We used a combination of lytic agent and PMT. In both instances of DVT overnight thrombolysis with tPA was beneficial. Angioplasty and stent deployment were further used for satisfac-

tory angiographic and clinical results, as demonstrated by immediate symptomatic relief on both occasions. As described in the literature, recurrent symptoms are common in patients in whom malignant disease is the causative factor. Our patient's findings at presentation echo this observation. This case underscores both pelvic radiation as a potential cause of iliac venous stenosis and endovascular intervention as the treatment of choice in patients with venous stenosis secondary to malignancy.

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Submitted Jan 25, 2004; accepted Mar 23, 2004.
Available online May 18, 2004.